Chapter 6: The Pharmacologic Modulation of Estrogen Receptor Activity

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Increased knowledge of the structure of ERs and of the mechanisms of the receptors' synthesis and their interaction with key elements of the transcription apparatus is facilitating the synthesis of new pharmacologically active molecules.

Key Points[a]

1. Cell specificity of estrogen action. Increased knowledge of the structure of ERs and of the mechanisms of the receptors' synthesis and their interaction with key elements of the transcription apparatus is facilitating the synthesis of new pharmacologically active molecules.
2. Pharmacologic modulation of ERs. Synthetic ER modulators can be classified as steroidal or nonsteroidal. Novel synthetic steroidal ER agonists hold promise for use in HRT because of agonist activity on the progesterone and androgen receptors. Of particular interest are the nonsteroidal agents that can act as SERMs by behaving as agonists in target tissues, such as bone and liver, and as antagonists or partial agonists in reproductive tissues [A and B].

1. Introduction

Natural estrogens modulate the activity of target cells by binding at least two intranuclear receptors. ERα and ERβ belong to a large family of structurally related transcription factors that are well conserved from the evolutionary and functional points of view.[1] The considerable progress made recently in comprehending ER structure (figs. 6–1 and 6–2) and mechanism of action (fig. 6–2) provides a basis for the development of new synthetic ligands aimed at modulating ER functions in an organ-specific fashion.

Transcriptionally inactive ERs reside in the target cell nucleus; they are generally bound to inhibitory proteins. Their activation can occur either by binding of the cognate hormone (ligand-dependent activation) or by posttranslational modifications (ligand-independent activation) that enable them to dissociate from the inhibitory proteins and associate with EREs, which are specific DNA sequences in the promoters of target genes.[2–7] Although currently little is known about ligand-independent activation of ERs, analyses of crystal structures of

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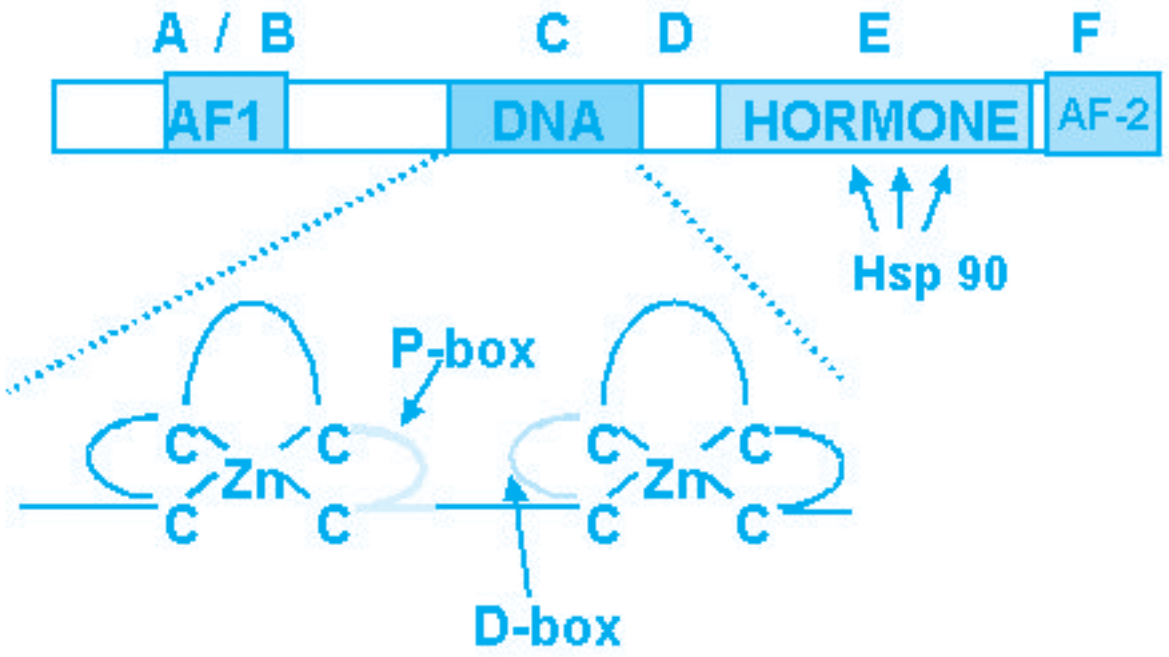
[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1).

FIGURE 6–1

Structural features of ERs. Mutation studies have identified six functional domains within the ER molecule (see ch. 5 for a more detailed description of ER functional domains): the N-terminal A/B domain, C domain, or DNA binding domain, D domain, the so-called "hinge region," and E/F domain, or ligand-binding domain. Ligand-independent AF-1 is located in the A/B domain, while ligand-dependent AF-2 is harbored by C-terminal E/F domain. C domain mediates the interaction between the receptor and the DNA through "zinc finger" structures.



the hormone-binding domains of ERβ and Erα complexed with agonists and antagonists provide some insight into the intramolecular modifications leading the ligand-receptor complexes to interact with the transcription machinery.[8,9] In addition, several coregulators involved in the generalized and tissue-specific activities of the receptors have been identified.[10–13] ERs may also influence the transcription of genes lacking EREs through binding other transcription factors (e.g., AP1) and thereby hindering these factors' capability to act on their responsive elements.[14,15]

2. CELL SPECIFICITY OF ESTROGEN RECEPTOR ACTION

It is now well known that estrogens produce a wide variety of physiologic effects and that ERs are expressed in most mammalian tissues. To design drugs able to mimic estrogen activity in only selected target tissues, it is mandatory to understand how the same hormone can exert so many different effects in the various cells targeted. One hypothesis is that the genes regulated by the hormone are different in each type of target cell. Because the hormone-receptor complex acts through the binding of the same EREs in all the cells, the question arises as to the factors determining the specificity of estrogen action. A number of

factors listed below may contribute, although, in spite of very active research in the field, more studies are needed to clarify which of the mechanisms predominate in the various targets.

Developmental Cues: During the process of cell differentiation, fragments of the genome are modified enzymatically or are bound by specific proteins and become inaccessible to transcription factors. The process will undoubtedly involve some of the ER-inducible promoters, which will become insensitive to the hormone activity.

Complexity of the Target Promoters: In complex promoters, in which different responsive elements control the transcriptional activity of a single gene, the activity of estrogens will be influenced by the presence of the other factors involved in gene transcription control.

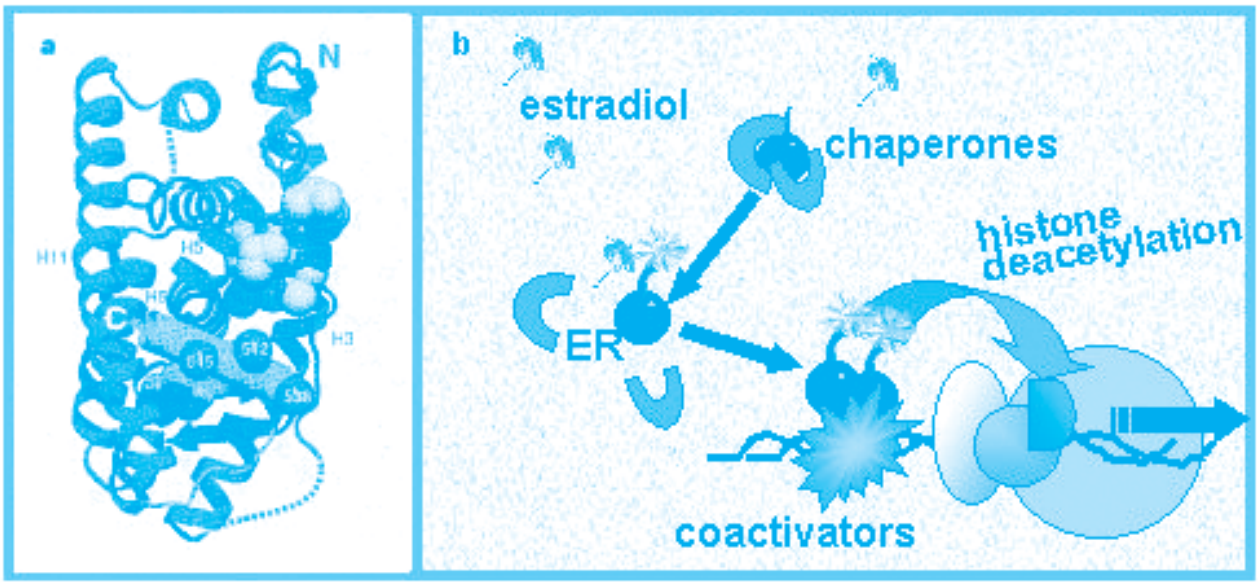
Tissue-specific Transcription Elements: As mentioned above, an ER must interact with transcription factors to initiate the transcription of target genes. The factors are in part ubiquitous and in part cell-specific. Therefore, the abundance of these cell-specific proteins will contribute to affect estradiol-ER action on individual promoters.

Receptor Dosage: Like other membrane receptors, ERs can be up- or down-regulated. It is most likely that higher concentrations of the receptor protein will allow the hormone to stimulate most of the target promoters, whereas lower concentrations will allow generation of subgroups of transcripts, for example, from genes whose promoters possess multiple EREs.

Ligand Characteristics: ERs bind estradiol and some of its metabolites. Depending on the ligand

FIGURE 6–2

Panel a. Graphic of the three-dimensional structure of the ER hormone-binding domain. The binding of the agonist induces a series of conformational changes that expose sites of the receptor capable of interaction with co-activators. The binding of antagonists induces a very different conformation of the receptor, mainly in the displacement of helix 12 (solid cylinder), and prevents the exposure of the domains involved in co-activator recruitment. Panel b. Mechanism of ligand-dependent activation of ERs. On binding to the receptor (ER), estradiol induces release of inhibitory proteins, which allow the receptor to dimerize and associate with the responsive elements in the promoters of target genes. Once bound to the target DNA, the receptor initiates a series of protein-protein interactions that result in the activation of the transcriptional apparatus.



bound, the conformation of the receptor differs, thus changing its functional activity.

To design drugs able to mimic estrogen activity in only selected target tissues, it is mandatory to understand how the same hormone can exert so many different effects in the various cells targeted.

Receptor Subtype: The type of ER expressed in a single cell type may also be important for the selectivity of estrogen action. In addition to the different effects exerted by ERα and ERβ homodimers, it is possible that ER heterodimers act differently and that the two receptors exert mutual control. That has been reported to occur with other members of the intracellular receptor superfamily.[16]

Influence of Other Members of the Nuclear Receptor Superfamily: Orphan receptors highly homologous to ERα—for example, ER-related receptors α, β, and χ may interfere with ER activities, also by heterodimerization.

3. Pharmacologic Modulation of Estrogen Receptors

Pharmacologic treatment of endocrine dysfunction involves the control of (1) endocrine signaling, by acting on the synthesis, storage, or release, or intracellular transport and metabolism, of the specific hormone; (2) sensitivity of a single target tissue to the hormone, by blocking or enhancing synthesis of the receptor of interest; or (3) activity of the receptor, by the use of specific ligands with agonist or antagonist activity. The synthetic compounds generated and in use to date for ER modulation belong to the third category, with the exception of progestins. In several organs, progestins antagonize the activity of estrogens by a dual mechanism: down-regulation of the synthesis of new ERs and control of the transcription of genes that interfere with estrogen action. Therefore, progestins are administered in combination with estrogens to limit the undesired side effects of estrogens on uterine cells.

The ligands for the ER can be grouped as ER agonists, ER antagonists and SERMs. Subgroups are based on chemical structure, categorized as steroidal and nonsteroidal compounds.

3.1 Estrogen Receptor Agonists

Known agonists of the ER consist of both steroidal and nonsteroidal molecules, with the latter including examples of different chemical structures.

3.1.1 Steroidal Agonists

Natural human estrogens are the follicular hormone 17β-estradiol and its main metabolites, estrone, estriol, and 2-hydroxyestradiol—together with their sulfated and glucuronidated counterparts. A more extended definition of natural estrogens includes the mare equilin and equilenin. Critical structural characteristics of this class of compounds include (1) a phenol at the C–3 position of the aromatic A ring, (2) a relatively flat and rigid hydrocarbon core, and (3) a ketone or alcohol function at the C–17 position. A detailed pharmacophore model suggests the important contribution of the two hydroxyl groups of 17β-estradiol to receptor binding, with C–3 hydroxy acting as the major contributor to the binding free energy. The model is supported by recent X-crystallography data.[8,9]

In replacement therapy, natural steroids are currently preferred over synthetic molecules.

When natural estrogens are administered orally, they undergo rapid catabolism in the intestinal mucosa and liver; shortly after estradiol ingestion, there are high concentrations of the metabolites, predominantly estrone, in the systemic circulation. Peak concentrations are observed at 1 to 4 hours after ingestion; subsequently, concentrations rapidly decline. For this reason, major efforts have been made, particularly

in the past, to synthesize steroid analogues of estrogens with longer half-lives. All the synthetic molecules developed are far more potent than the natural estrogens and have, when administered orally, much longer half-lives. Some, like DES are no longer used in clinical practice. The finding of a high incidence of clear cell adenocarcinoma of the vagina in daughters born to DES-treated mothers led to the hypothesis that the compound was a carcinogen. However, further studies did not show a significant increase in breast cancer in the DES-treated mothers, and studies of male offspring showed genital abnormalities, suggesting that DES should be considered more as teratogenic than cancerogenic. Other synthetic estrogens, such as ethinyl estradiol, have been and are largely used in oral contraception. Ethinyl estradiol is obtained by the addition of an ethinyl radical in position C–17 and is much more resistant than natural estrogens to liver metabolism. Orally administered ethinyl estradiol has a half-life of about 48 hours.

In replacement therapy, natural steroids are currently preferred over synthetic molecules. In the United States, the most commonly used natural estrogens are CEEs, extracted from the urine of pregnant mares. CEEs are mainly composed of estrone and estrone sulfate; other components include the ring-B unsaturated sulphoconjugated estrogens equilin, equilenin, and their 17α-derivatives. The metabolites account for a great part of the estrogenic effects of CEEs. In addition, equilin can be stored in adipose tissue and released for several weeks after withdrawal of the treatment. 17β-estradiol is also used in HRT, particularly in Europe. Preparations of estradiol valerate or micronized estradiol were shown to have half-lives compatible with therapeutic effects when administered orally.[17] To avoid the intensive first-pass metabolism, nonoral routes of administration of 17β-estradiol have been studied. Several parenteral delivery systems are available: 17β-estradiol can be administered through injections, vaginal rings, percutaneous gels, or transdermal therapeutic systems (TTS). Of particular interest are the TTS that allow the rate-controlled delivery of estrogen. The hormone is suspended in an ethanol solution or, in second-generation TTS, in a matrix, which ensures the programmed release of the hormone for several consecutive days.

More recently, novel synthetic molecules such as (7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)en-20-yn-3-one (tibolone) have raised considerable interest because they combine with the estrogenic activity progestogenic and androgenic properties that relieve climacteric symptoms without stimulation of the endometrium.[18,19]

Observational epidemiologic studies indicate that women who ingest phytoestrogens, particularly in soy products, in large amounts seem to have lower rates of CVD, breast cancer, and uterine cancer as well as fewer climacteric symptoms than women consuming typical western diets.

3.1.2 Nonsteroidal Agonists

Pioneering studies published more than 60 years ago showed the effects of subcutaneous administration of nonsteroidal compounds on the onset of estrus in mammals and on uterine growth. They enabled the identification of several nonsteroidal molecules with estrogenic activity. The studies were also instrumental in the subsequent development of antiestrogens and of partial agonists-antagonists, including SERMs.

The major categories of the nonsteroidal agonists are (1) 1,2-diarylethanes and ethylenes; (2) flavones, isoflavones, coumestans, and lignans; (3) macrolactones; (4) alkylphenols and arylphenols; and (5) nonaromatic estrogens.

1,2-Diarylethanes and Ethylenes: DES and hexestrol (fig. 6–3) represent a milestone in the identification of orally active nonsteroidal agents

with extremely potent estrogenic activity. The medical uses of compounds with 1,2-diarylethylene and 1,2-diaryl ethane include maintenance of pregnancy, HRT, suppression of lactation, postcoital contraception, and cancer treatment, as has been reviewed.[20]

Flavones, Isoflavones, Coumestans, and Lignans: The best studied plant-derived estrogens, or phytoestrogens, belong to these classes of chemicals with estrogenic activity. A significant source of isoflavones is soybeans. The most abundant and active components of isoflavones are genistein (fig. 6–3) and daidzein, which appear to have selective estrogenic actions. In some tissues, they provoke proestrogenic responses; in others, they inhibit estrogenic effects. This finding is perhaps explained by different affinities for the two described ERs. Indeed, genistein has a thirtyfold higher affinity for ERβ than for ERα.[21,22] The estrogenic activity of flavones and isoflavones is dependent on ER binding affinity, which is determined by the presence of the aromatic ring as well as hydroxyl groups at specific sites.

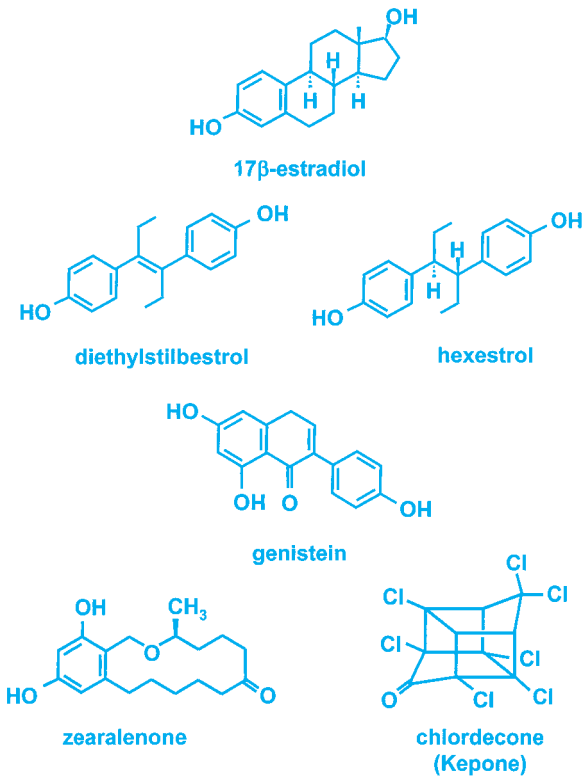
Compared with estradiol, genistein and daidzein bind to ERs with significantly less affinity.[23] Nevertheless, in the quantities that can be consumed in the diet, isoflavones can have biologic effects. Soybean isoflavones do not have feminizing effects in male primates as reflected by unchanged weights of the reproductive organs in the animals,[24] although prenatal exposure of rats resulted in diminished weights of ovaries and uteri.[25] Observational epidemiologic studies indicate that women who ingest phytoestrogens, particularly in soy products, in large amounts seem to have (1) lower rates of CVD, breast cancer, and uterine cancer and (2) fewer climacteric symptoms than women consuming typical western diets.[26] (See ch. 3, 8, and 10.) Preclinical and clinical studies have shown that isoflavones can improve plasma lipid profiles as well as the ability to inhibit oxidation of low-density lipoproteins.[26] Isoflavones have been shown to normalize vascular reactivity in estrogen-deprived primates.[27] Antineoplastic activity of the compounds has been postulated on the basis of their inhibitory activity on angiogenesis.[28] In addition to climacteric symptoms, bone density appears to be favorably influenced by phytoestrogens.[26] (See also ch. 9.)

Other known phytoestrogens are coumestans (e.g., coumestrol), found in alfalfa sprouts, and lignans (e.g., enterolactone), found in cereals and oil seeds such as flaxseed.

Macrolactones: Macrolactones were first identified when hyperestrogenicity was seen to develop in swine fed mold-infected corn. Katzenellenbogen and colleagues extensively studied these mycotoxins, exemplified by zearalenone (fig. 6–3), which was shown to bind ERs with high affinity and induce uterotropic responses in rats.[29] Zearalenone has been used to relieve the incidence and severity of hot flushes in women.[30]

FIGURE 6–3

Structural Characteristics of Estrogen Receptor Agonists



Alkylphenols and Arylphenols: Alkylphenols are used in the synthesis of detergents and as antioxidants. The detergents are not estrogenic; upon degradation during sewage treatment, however, they can release estrogenic compounds, such as para-octyl phenol and para-nonyl phenol, which have been shown to possess uterotropic activity in vivo and in vitro.[31] The structural requirements of alkylphenols indicate that both the position (para > meta > ortho) and the branching (tertiary > secondary) of the alkyl group dramatically affect estrogenicity.[32] In addition to alkyl substitution at the para position of the halogenated or the hydroxy-substituted aromatic ring, aryl substituents have estrogenic activity. Compounds in the class include bisphenol A; polychlorinated biphenyls; diphenylmethanes, such as DDT (dichlorodiphenyltrichloroethane); and tricyclic aromatic hydrocarbons, such as dioxin.[33] Many of these compounds are used in the manufacture of plastics, and their estrogenic activity was discovered by accident because they are released by polystyrene and polycarbonate test tubes used in laboratory experiments. Bisphenol A was found to contaminate the content of canned food because tin cans are lined with polycarbonate. Bisphenol A is also used in dental sealants and composites.

Nonaromatic Estrogens: Interest in nonaromatic estrogens has increased because xenoestrogens of this class can derive from commercial sources, such as pesticides. Most of the agents are halogenated carbocycles, such as hexachlorocyclohexane, chlordecone (Kepone) (fig. 6–3), chlorobornane (Toxaphene), dieldren, and endosulfan. Studies with hexachlorocyclohexane showed it to have estrogen agonist activity in human breast cancer cell lines. It and others of the class have not been shown to bind to ERs. Therefore, the origin of the estrogen activity of the compounds is not clear; it is believed to occur through nonclassic pathways.[34]

3.2 Estrogen Receptor Antagonists

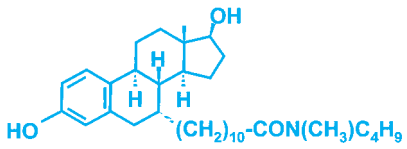
Antiestrogens can be grouped according to basic structure as steroidal or nonsteroidal.

3.2.1 Steroidal Antagonists

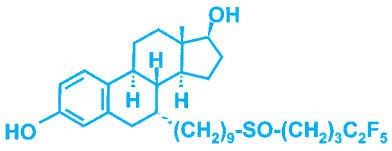
The difficulty in modifying the basic steroid structure discouraged research into steroidal antagonists of ERs until Raynaud et al. demonstrated that the 7α-estradiol derivatives with a long, unbranched alkyl chain retained high affinity for ERs.[35] The compound ICI 164,384 was developed and shown to act as a pure ER antagonist, stimulating further research. The most active compounds that emerged from the studies are ICI 164,384 and ICI 182,780 (fig. 6–4a). Both avidly bind to ERs and retain a pure antiestrogen activity in all tissues studied to date.

FIGURE 6–4a

Structural Characteristics of Estrogen Receptor Antagonists



ICI 164,384



ICI 182,780

3.2.2 Nonsteroidal Antagonists

For the rational design of nonsteroidal antiestrogens, essentially two basic structures were systematically altered: the triphenylethylene and stilbene structures. The first nonsteroidal antiestrogen discovered was ethamoxytriphetol (MER–25) (fig. 6–4b).

Its potency as an antiestrogen was rather low, and serious side effects in the CNS were found during clinical development.[36] The antagonist activity of the molecule may be due to the hydrophilic hydroxy group in the center of the molecule, which most likely interferes with the receptor binding. Clomiphene (fig. 6–4b), the second ER antagonist developed, lacks the central hydroxy group, and a double bond with a chloro substituent improves its lipophilicity. Clomiphene is used as a gonad-stimulating agent in subfertile women. With the identification of the ER antagonist activity of nafoxidin (fig. 6–4b), it became evident that a certain steric arrangement at the double bond favors the antiestrogenic activity. The most prominent among the group of drugs is tamoxifen, which was developed by ICI and is marketed as a citrate salt. The activity of tamoxifen in postmenopausal patients with hormone-dependent breast cancer has been demonstrated in many clinical studies, and the agent has become a treatment of choice for the malignancy. Tamoxifen is used in patients with advanced disease, as well as in the adjuvant setting after surgical removal of the primary tumor.

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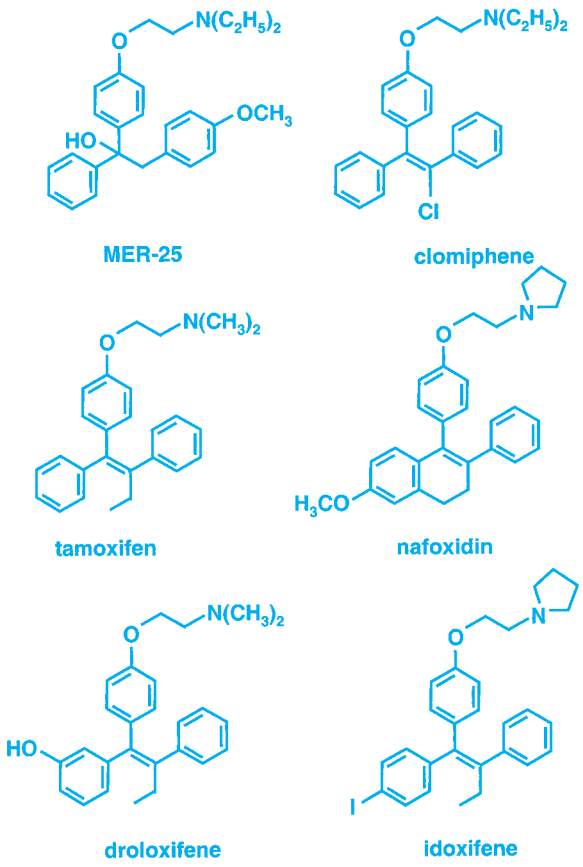
Other triphenylethylene derivatives were synthesized with the objective of obtaining an antiestrogen that would have a lower rate of metabolism and a different pharmacodynamic profile compared with tamoxifen and would not present its cis/trans isomerization. The knowledge that 4-hydroxytamoxifene is more potent in vitro than the parent drug but is more readily catabolized provided the basis for the development of the 3-hydroxy derivative droloxifene and of the iodo derivative idoxifene (fig. 6–4b). Droloxifene and idoxifene were

FIGURE 6–4b

Structural Characteristics of Estrogen Receptor Antagonists



shown to have minimal uterotropic activity, to reduce plasma cholesterol concentrations, to stimulate osteoclast apoptosis, and to block gene expression in endometrial cells.[37] Despite the fact that the basic side chain is one of tamoxifen's most important structural elements, only a very limited number of variations of that part of the molecule have been synthesized. Interestingly, when the 2-(dimethylamino)ethoxy fragment was replaced by acrylic acid, the agonist activity was lost in the uterus but was retained in bone and the cardiovascular system.[38]

Studies carried out principally at Eli Lilly and Company demonstrated that the geminal arrangement of the two phenyl rings of tamoxifen is not

essential and can be replaced by structures in which all three phenyl groups are located at different atom groups. Several compounds were generated (fig. 6–4c), among them LY 117,018, the first to undergo detailed study of its endocrine activities.[39] A series of modifications of LY 117,018 led to the synthesis of keoxifene (LY 156,758), which is now known as raloxifene.[40] In raloxifene, the presence of two free hydroxy groups in the benzothiophene and phenyl rings gives rise to an ER-binding affinity higher than in compounds lacking those polar functions.

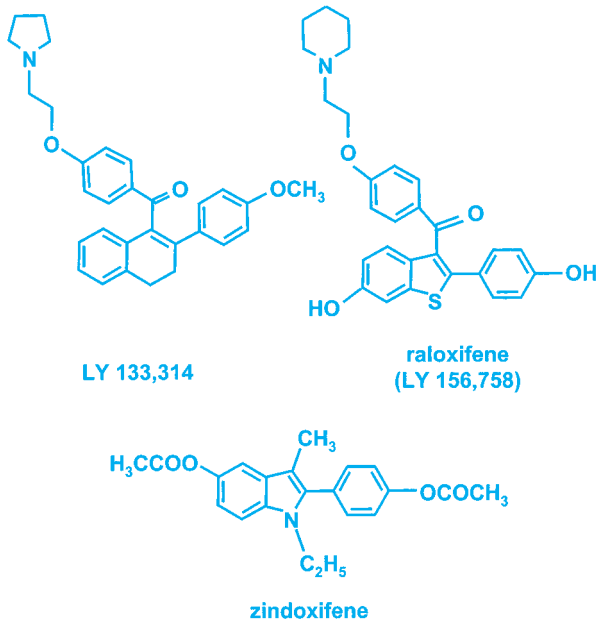
Another basic structure that has been utilized for the rational design of antiestrogen drugs is 2-phenylindole. Zindoxifene (fig. 6–4c) belongs to the compounds synthesized with this structure. Its endocrine profile is that of an antiestrogen with partial agonist activity. The preclinical and clinical data thus far obtained suggest that zindoxifene is a new lead structure of interest for the design of drugs acting through ERs.

3.2.3 Estrogen Receptor Subtype–Specific Antagonists

The substantial structural homology between ERα and ERβ has raised the question of whether the two receptors are, indeed, responsible for different physiologic responses. Localization studies performed in mature and developing mammals suggest different roles for the two receptors. In fact, ERα and ERβ are often differentially expressed in developing and mature tissues (e.g., mammary gland and brain) and seldom colocalize in a given cell type.[41] Ablation of one or the other of the two receptors in gene knockout experiments further supports the hypothesis of a different effect of the two receptors. ERα activity seems to predominate in the uterus and breast, whereas ERβ may have significant roles in the CNS, cardiovascular system, immune system, urogenital tract, kidney, and lung. (See also ch. 5.) ERβ appears to be the only form expressed in the embryonic CNS.[42–44] On the other hand, the two receptors can co-localize; it is possible that they form heterodimers, the transcriptional activity of which may significantly differ from the homodimers.[45,46] Finally, in vitro studies evaluating the response of reporter genes or more physiologic parameters of pharmacologic activation of the two receptors have demonstrated significant differences between ERα and ERβ activities. In spite of the remarkable similarity in their response to synthetic ligands, the two receptors seem to activate distinct target genes, with divergent consequences for cell physiology.[47,48] The differential activity can be attributed to the significant structural diversity of the A/B region carrying the ligand-independent, N-terminal activation function AF–1. This hypothesis is supported by studies with a chimera receptor in which the A/B domain of ERα was substituted to the same domain of ERβ.[49] Thus, because of the potential physiologic differences in the activities of the two receptors, differences in ligand interaction or activity could translate into important differences in their biological and pharmacological profiles.

FIGURE 6–4c

Structural Characteristics of Estrogen Receptor Antagonists



The observation that the degree of homology of the two hormone-binding domains of ERα and ERβ is approximately 56 percent suggests the possibility of developing ligands with different agonist or antagonist characteristics with regard to the two receptor subtypes. Recently, novel compounds with pronounced subtype-selective differences in binding affinity and transcriptional potency or efficacy were identified.[50] An aryl-substituted pyrazole was shown to be an ERα potency-selective agonist: in fact, it showed a higher binding affinity for ERα than for ERβ and, in transactivation assays, a potency of ERα of about two orders of magnitude higher than ERβ.

Another compound, a tetrahydrochrysene (THC), was shown to have a fourfold preferential binding affinity for ERβ; it was an agonist for ERα and a complete antagonist for ERβ. Interestingly, the antagonist activity appeared to be associated with the R,R-enantiomer (R,R-THC); the S,S-THC was an agonist for both ERα and ERβ but had a twentyfold lower affinity for ERβ than R,R-THC.

3.2.4 Molecular Mechanisms of Antiestrogen Action

The molecular mechanisms of antiestrogen blockade of ER activities have been the object of several studies addressing all the steps necessary for ER transcriptional activation.

Receptor Binding: Generally, the affinity of antagonists for ERs is similar to or even higher than the affinity of estradiol. It was initially proposed that the binding of an antagonist, in particular the binding of pure antagonists,[51] prevents the dimerization and limits the affinity of the complex for DNA. Those studies were highly controversial, and the mechanism cannot be extended to tamoxifen, which was clearly shown to allow the formation of ER dimers.[52]

DNA Binding: Most in vitro studies have shown that DNA binding activity of the ER complexed with agonists and antagonists is very similar, even though the DNA binding of antagonist-ER complex seems to be slower than that of agonist-ER complex. Dissociation of the former complex is much slower than dissociation of the latter.

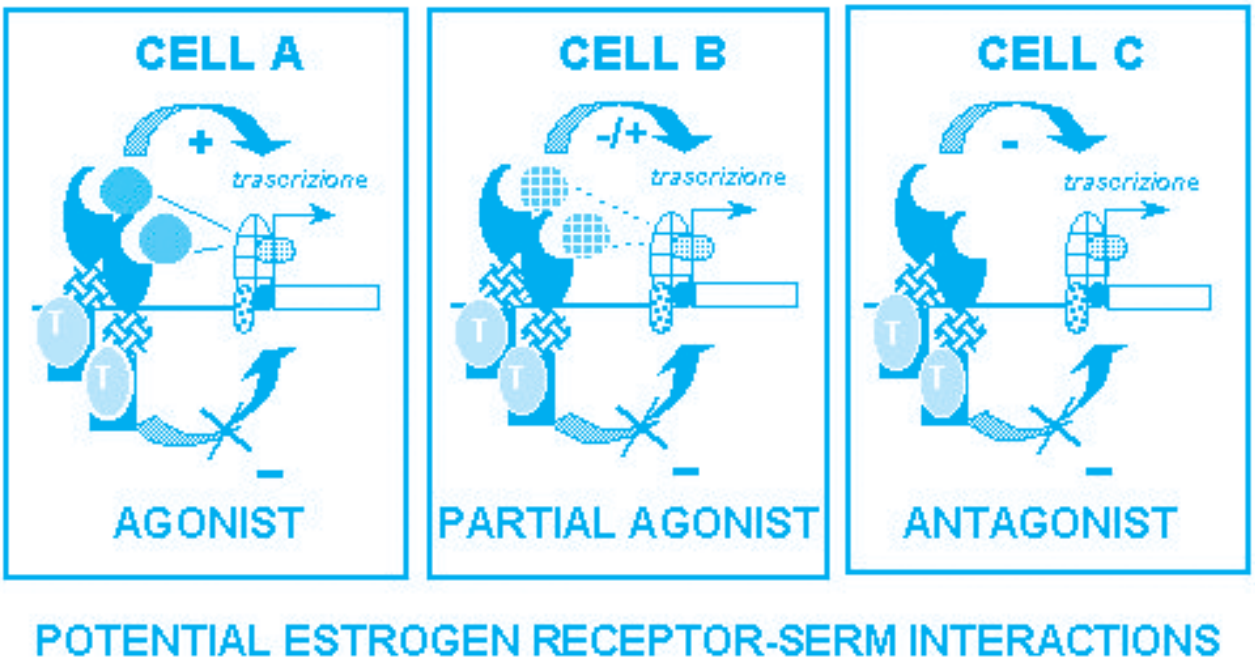
Protein-Protein Interaction: The availability of crystals of the ERα and ERβ hormone-binding peptides bound to 4OH-tamoxifen and raloxifene provides important new information about the mechanism of these agents' activity. Studies show that the additional side chain of the antagonists protrudes from the ligand-binding cavity, so that helix 12 is translocated to a position in which the co-activator binding side is obscured. As a consequence, the antagonist-ER complex can still dimerize and bind to DNA, but this event cannot be followed by the series of protein-protein interactions indispensable for AF–2-dependent transcription initiation, mediated through ligand-dependent, C-terminal activation function.

Those findings underline the importance of protein-protein interactions (ER with co-activators or co-repressors) in the mechanism of action of ER antagonists. Furthermore, they provide an explanation for the mixed agonist-antagonist activity reported for both raloxifene and tamoxifen bound to ERα. (See fig. 6–5.) In fact, the binding of this antagonist prevents interactions of AF–2, but not AF–1, with the transcription machinery. Therefore, the receptor, once bound to the ERE, may still attract transcription factors with the AF–1 region and allow the transcription of selected genes. Deletion and mutation studies have demonstrated that the full transcriptional activation of ERα is observed when both AF–1 and AF–2 are present and activated.[53] When access to AF–2 is prevented by the presence of an antagonist, the activity of the receptor is limited to those cells and those promoters that contain factors that activate AF–1. (See also ch. 5 for mechanisms of differential actions of antagonists on ER subtypes α and β.)

Receptor Turnover: ER antagonists may affect the kinetics of ER degradation. This represents another potential mechanism of action of antago-

FIGURE 6–5

Mechanism of action of SERMs in different cell settings. Binding with a SERM results in blockage of activity of the AF–2 region of the ER; the AF–1 region, however, is free to interact with other proteins, which allows the interaction of the DNA-bound ER with other elements of the transcription apparatus. Thus, depending on the proteins expressed in the host cell, the SERM-bound receptor will be able to act as a full agonist (cell A) or a partial agonist (cell B). In cells that lack proteins able to interact with the AF–1 region of the receptor, the SERM will completely prevent the activation by estrogens and, therefore, will be a complete antagonist (cell C).



nists; it has been shown to be of importance for pure ER antagonists, such as ICI 164,884 and ICI 182,780, but not for nonsteroidal antagonists.[54]

3.3 Selective Estrogen Receptor Modulators (SERMs)

A SERM is defined as a compound that has estrogen agonism in one or more of desired target tissues, such as bone and liver, and antagonism and/or minimal agonism in reproductive tissues such as breast and uterus.[55]

The path leading to SERM development began with the synthesis of the first nonsteroidal estrogen antagonist, MER–25, which was shown to inhibit the action of estradiol in the endometrium without itself causing endometrial stimulation. Later, the nonsteroidal triphenylethylene compounds clomiphene citrate and tamoxifen were reported to be capable of inducing ovulation by blocking the negative feedback of estradiol on the HPA[56,57] and to block the development of dimethylbenzanthracene-induced mammary tumors in rats[58] (tamoxifen). The results clearly demonstrated the antiestrogenic activity of the molecules and stimulated interest in their development for antineoplastic activity. In the 1980s, two seminal studies, by Beall et al.[59] and Jordan et al.,[60] demonstrated that clomiphene and tamoxifen had a more varied portfolio of action in that the agents were able to decrease bone loss in ovariectomized rats. The

findings were remarkable because a pure antiestrogen would have been expected to promote rather than inhibit bone loss. Because clomiphene is a racemic mixture of enclomiphene and zuclomiphene, primacy in the SERM field must be accorded to tamoxifen. However, the discovery that tamoxifen was, in some patients, capable of endometrial stimulation leading to hyperplasia or neoplasia[61] precluded its development as a bone antiresorptive agent that would be free of uterine bleeding and, it was hoped, breast safe.

The concept of selective ER modulation has been demonstrated subsequently for a number of compounds, including raloxifene, droloxifene, GW5638, idoxifene, and FC–1271. Toremifene and idoxifene are molecules similar to tamoxifen; despite their potential as SERMs, they have been targeted for the treatment of advanced breast cancer. Droloxifene is known to have efficacy as a breast cancer drug but is also a SERM at bone sites.[62] Raloxifene was developed because it held promise for multiple applications. It is used in the prevention of bone loss and fracture in postmenopausal women and is being tested against tamoxifen in the Study of Tamoxifen and Raloxifene (STAR) for the prevention of breast cancer in high-risk postmenopausal women.[63] Additionally, raloxifene reduces circulating cholesterol concentrations[64] and may be efficacious to reduce risk for endometrial cancer.[55] The main drawback of the drug is that it does not reduce the occurrence of hot flushes, which could hinder compliance. Similar pharmacologic profiles are shared by idoxifene and FC–1271, which were shown to have beneficial effects on bone metabolism in rat models and to act like estrogens in bone and on circulating lipoprotein concentrations, with little estrogenic activity in the uterus.[37,65] A number of SERMs are in preclinical or clinical development (table 6–1).

The molecular mechanisms of the different effects of SERMs in different organs are summarized above (“Molecular Mechanisms of Antiestrogen Action”) and in figure 6–5.

The challenge for the future in the development of ligands for the ERs will be to refine the target specificity of SERMs and, it is hoped, amplify their scope of action. For instance, a SERM with a profile similar to idoxifene or raloxifene in the peripheral organs and CNS might protect against Alzheimer’s disease and hot flushes, while helping prevent osteoporosis, CAD, and breast and endometrial cancers.

4. Future Needs

The availability of drugs selective for ERα and ERβ will constitute a major milestone toward the development of drugs with specificity of action. On the other hand, the acquired knowledge of the molecular mechanisms of estradiol activity in different cells might suggest novel paths to be followed for the development of molecules active through the ERs. For example, ER turnover is differentially regulated in various organs (e.g., following gonadectomy, ERα mRNA is increased in the uterus but significantly decreased in the liver[66]). Drugs aimed at modulating the synthesis of ERs in specific organs may enable fine tuning of the activity of the hormone. Antisense oligonucleotides have been able to block ER synthesis in cells in culture. The development of such molecules as drugs might allow their future clinical use.[67] Alternatively, novel preparations of estradiol in which its bioavailability is modified might have pharmacologic profiles of interest. For instance, a formulation allowing a very rapid intraplasmic release of estradiol and its rapid clearance (e.g., transnasal administration of appropriately modified estrogens) could have a quite different profile of action compared with estradiol administered orally or transdermally. Such a drug could rapidly activate the receptors but, because of its rapid clearance from the blood, might have little effect on ER down-regulation or might affect it differently in the various targets.

TABLE 6–1

Selective Estrogen Receptor Modulators Under Development

Drug	Pharmaceutical Company	Phase of Development	Therapeutic Class
SERM 339	Aventis	Phase IIa	
HM 144	Hormos Medical	Preclinical	Anti-Alzheimer
LY 139,478	Eli Lilly and Company	Preclinical	Bone calcium regulation
LY 326,391	Eli Lilly and Company	Preclinical	Cytostatic, bone calcium regulation
ERA 932	Ligand Pharmaceuticals	Phase I	Cytostatic
NNC 450,320	Novo Nordisk	Preclinical	Bone calcium regulation
NNC 450,781	Novo Nordisk	Preclinical	Bone calcium regulation
M.D.L 101,986	Aventis Pharma	Preclinical	Cytostatic, bone calcium regulation
Fc1271A	Hormos Medical	Phase II	Other drugs for the musculoskeletal system
Arzoxifene	Eli Lilly and Company	Phase II	Cytostatic
Research program SERMs	Signal Pharmaceutical	Preclinical	Cytostatic, bone calcium regulation
Lasozifene	Pfizer	Phase II	Bone calcium regulation
Research Program SERMs	Ligand Pharmaceuticals /Pfizer	Preclinical	Cytostatic, bone calcium regulation, anti-Alzheimer
SR 1,634	SRI International	Preclinical	Cytostatic

Recently, the use of phage display has allowed the identification of peptides that interact specifically with estradiol- or tamoxifen-activated ERα. Some peptides were shown to regulate ER transcriptional activities.[68] Such studies demonstrate that ER activity can be regulated even by targeting sites that are outside the ligand-binding pocket of the protein. This is not surprising within the current view of ER interactions with other proteins relevant in transcription. Such results have pharmacologic implications of interest because they provide new targets for drug activities and more opportunities for the development of drugs that will modulate the activity of ERs in selected cells or even at specific genes. Finally, increased knowledge of the physiologic relevance of unliganded activation of ERs might lead to the development of pharmacologic compounds that will activate ERs through membrane receptors.

These and other molecular developments will in the near future represent starting points for the preclinical and clinical development of estrogen compounds, of both natural and synthetic origins, with selective spectrums of action, as the following points summarize:

- Developing drugs with receptor specificity (ERα or ERβ)
- Modulating the activity of the hormone interfering with the synthesis of ERs
- Attaining different profiles of action for exogenous estradiol through use of different formulations
- Obtaining higher specificity of action by identification of new target molecules involved in gene transcription
- Increasing knowledge of the mechanisms involved in ER activation through membrane receptors to develop new pharmacologic compounds acting along these pathways

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Chapter 7: Sexuality

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Declining sexual function is common with aging. There may be an additional decrement associated with the menopausal transition.

Key Points[a]

1. Declining sexual function is common with aging. There may be an additional decrement associated with the menopausal transition.
2. The causes of decreased sexual activity are multiple and include physiologic, psychologic, and social factors.
3. Definitions and Classification of Female Sexual Dysfunction, given by the consensus panel of the Sexual Function Health Council of the American Foundation for Urologic Disease, provide a standardized system for clinical diagnosis and treatment and are recommended for use by health care professionals [D].
4. Sexual interest, behavior, and activity should be routinely assessed at office visits on a regular basis, and a plan should be developed to address the woman's concerns.
5. Hormonal and behavioral therapy have had variable success in the treatment of sexual dysfunction but should be considered in patients who desire treatment for their dysfunction [B].

1. Introduction

"Sex is a biologic expression of love and part of a universal human behavior with roots stretching back to the beginning of humankind."

Won-whe Kim, M.D., Ph.D.

As women live longer, are healthier and more educated, have more leisure time, and are more aware of their own sexuality, they become inquisitive and sometimes apprehensive about changes in sexual function after menopause. Sarrel and Whitehead,

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.)

in their survey of postmenopausal women, found a high prevalence of sexual problems, corroborating these changes in sexual function after menopause.[1] When women experience changes in their sexual function, they frequently turn to their health care provider for help with their problems.

The prevalence of female sexual disorders, in both premenopausal and postmenopausal women, ranges from 25 to 63 percent.

The prevalence of female sexual disorders, in both premenopausal and postmenopausal women, ranges from 25 to 63 percent.[2–4] The recently published U.S. National Health and Social Life Survey included survey data from 1,749 women between the ages of 18–59 years (table 7–1).[5] Sexual dysfunction was more prevalent in women (43 percent) than men (31 percent). One-third of women lacked sexual interest, and almost one-fourth stated that they were unable to experience orgasm in menopause. According to the survey, 20 percent of those women reported lubrication difficulties, and another 20 percent reported that sex provided them little pleasure. Relevant to this survey, sexual dysfunction appeared to be more common in menopausal women than in premenopausal women. Similarly, more than 86 percent of postmenopausal women in Sarrel and Whitehead's survey reported a variety of psychosexual problems.[1] Due to the high prevalence of sexual dysfunction and the importance that patients attach to sexual function, it is essential to identify and address these problems in our patients. Ultimately, it will assist them in improving their quality of life and interpersonal relationships.

Much attention has been given to male sexual dysfunction, and only recently has attention shifted to better understand and identify female sexual dysfunction as a research priority. Clinicians receive little or no training in the diagnosis or treatment of sexual dysfunction and lack information on its causes and ways to prevent the changes that may occur. The clinician's individual clinical impressions and previous experience are frequently used as the basis for clinical practice and are conveyed to the patient as truth, without evidence to support those views. Regrettably, most practitioners' clinical experience is not representative of most women's experience in the menopause. This is in part because those presenting for treatment are only a small proportion of women troubled. Those who choose to identify themselves to the clinician as having a problem represent only a fraction of women with problems.[6,7] Armed with the appropriate facts, the clinician will be rewarded because all patients appreciate clinician awareness and competency in this field.

Because of these barriers, many studies in this review have methodologic weaknesses, including sample bias, low measurement sensitivity, and lack of detail on sexual preference. Population-based surveys suggest a link between menopause and changes in sexuality. Yet, relatively few studies of the menopausal transition in middle-aged women have inquired about sexual functioning. Of those, only a minority have used a validated questionnaire to assess the different aspects of sexual functioning. In addition, cross-sectional studies are unable to distinguish between effects of social change on different age groups and aging, and some improperly infer causation from associations. (See also ch. 3, sec. 3.)

Not insignificant is the controversy surrounding the study of sexual relationships. Kim noted that in some ethnic groups it is almost impossible to get an accurate answer from women about their sexual activities (Kim WW, personal communication). He accurately commented that there are very few norms set biologically or statistically, and, as a consequence, analyses done with questionnaires and interviews might not be reliable. Some interviewees are not sincere in answering the questions, and some give false information, as they feel shy about presenting their thoughts and feelings frankly. He emphasized that in most Asian countries,

TABLE 7–1

Prevalence of Female Sexual Disorders (Percent of Women)

	Lacked Interest in Sex (n = 1,486)	Unable to Achieve Orgasm (n = 177)	Experienced Pain During Sex (n = 1,479)
Age (years)			
18–29	32	26	21
30–39	32	28	15
40–49	30	22	13
50–59	27	23	8
Marital Status			
Currently married	29	22	14
Never married	35	30	17
Divorced, separated, widowed	34	32	16
Race			
Caucasian	29	24	16
Black	44	32	13
Hispanic	30	22	14
Other	42	34	19

where over half the world's population lives, the situation is even more complicated. Women are raised under the influence of Confucian ideology from early childhood and are taught that they should not even be allowed to express their desire to have sex. All the myths and misconceptions concerning female sexuality, especially in old women, remain. They believe, "It is natural to be away from sex when you are old" or "Remarriage after the death of your spouse should never be thought of."

Population-based surveys suggest a link between menopause and changes in sexuality.

Other methodological problems limit study in this field. Until recently, there were no objective, standardized definitions of both the physiologic and psychologic basis of female sexual dysfunction and menopause. On the other hand there is still no consensus on an age cohort that covers the menopausal transition. Should it be 45–55 years of age, or should it be defined by shorter intervals? There are differences between naturally and iatrogenically induced menopausal women and these distinctions are often not made in discussions of sexual dysfunction. Furthermore, the differences between those who choose to take exogenous hormones and those who wish to make the menopausal transition without pharmacotherapies are not well defined. Therefore, how we approach these women differently is confusing. Objective measures of hormonal change are not defined or standardized; instead, the absence of uterine bleeding repeatedly defines menopause. (See ch. 2 for definitions.) Questionnaires are not designed to reflect how women experience, problems and data analysis techniques have to be more appropriate. (See ch. 3 and 4 for biases in women sampling.)[8] The studies reviewed in this chapter represent the available current evidence and must be used as a basis for best practice.

This chapter is designed to provide the best answers to the following questions based on the current evidence in the literature:

- Do changes in sexual behavior, interest, or response, occur with age or menopause, or both?
- If changes occur, what are they, and what causes them?
- How do we define the changes?
- Do we treat the changes, and if so, what therapies have proven efficacy?

2. Influence of Age on Sexuality

The most frequent measures of change in sexual function used in the literature are coital and orgasmic frequency. To understand the changes of the menopausal transition, we must first review the changes leading up to the years most commonly used to define menopause.

The Kinsey studies conducted in the 1950s were the earliest to examine the relationship between sexuality and age. In 1953, in a cross-sectional descriptive analysis, Kinsey et al. described the aging patterns of sexual activity in unmarried men and women.[9] The frequency of orgasm reported by women remained relatively constant at 0.5 episodes per week from puberty through age 55. Men reported a constant decline from 2.3 episodes per week at age 15 to 1 episode per week at age 50. Married women and men showed similar declines in frequency, with women having lower levels of activity than men at all ages. The authors surmised that the married woman's decline might be a result of her husband's and not her own aging. Women also indicated that their sexual activity reflected whether or not they had a partner and, if they did, their partner's preferences. Their report lacks indication of a decline in a woman's sexual function secondary to age, and it was unable to determine whether a decline in function with age was due to physiologic, psychologic, or social factors.

A legitimate question to ask is whether this information obtained from two generations past applies today. The answer awaits further study. There have clearly been changes in sexual mores over the years. Nowadays, the orgasmic frequency of women may be much higher than 0.5 episodes per week. Many women experience orgasm in different ways than is classically described, and this may explain the relatively low frequency of orgasm reported in the Kinsey studies. Moreover, many women get sexual satisfaction without achieving orgasm, especially those who value intimacy and the relationship with their partner. This is often not accounted for in research studies.

Some of the earliest studies of sexuality attempted to define the factors that influenced sexual activity. In 1960, Newman and Nichols reported cross-sectional data on 250 men and women between the ages of 60 and 93.[10] In the 100 persons in the single, divorced, or widowed group, only 7 percent were sexually active. In the remaining 150 persons in the married group, 54 percent were sexually active, suggesting that a socially permitted and legally approved partner significantly influenced the continuance of sexual activity. There was a gradual decline in activity through adulthood, although some level of activity persisted into late adulthood.

In 1972, Pfeiffer et al. attempted to report the various sexual behaviors in middle-aged and older both women and men.[11] Using a subsample from a larger longitudinal study on the determinants of adaptation in middle life (the Duke study), they showed a pattern of declining sexual activity with age in both sexes. The frequency of intercourse was lower for women than for men at all ages; however, 98 percent of the men versus 71 percent of the women were married. Both women and men attributed the choice of discontinuing sexual intercourse to the man. Only 7 percent of women reported no sexual interest. Of those who did note a decline, the sharpest increases were noted between ages 45 and 50 and between ages 51 and 55. These findings contradicted earlier work.

In 1981, George and Weiler reported on 502 married men and women 46–71 who were followed from the original Duke cohort at 2-year intervals for 4 years.[12] Of those who attended all interviews and remained married (278), 20 percent of the total group reported a decrease in sexual activity while 5 percent reported an increase. Only a small portion of the sample (n = 57) were women aged 46–55 at the beginning of study. Despite the overall decrease, the authors concluded that sexual activity remained more stable over time than was previously suggested. One limitation of the Duke Study was that it obtained its sample from enrollees of an insurance company and was therefore a biased sample of middle, and upper-class healthy, employed people 55 years and older.

As evidenced by the above reports, there had been only small, descriptive reports up to the late 1970s. This led Hallstrom to recruit 800 perimenopausal Swedish women aged 46, 50, and 54 years and a premenopausal group, 38 years of age to attempt to better define changes in sexual functioning which may be related to the menopausal transition.[13] All of the women had intact uteri and ovaries, and none were using oral contraceptives (OCs). All were cohabiting with a man. Factors assessed were sexual interest, orgasm with coitus, change in sexual interest, change in capacity for orgasm, and mean frequency of coitus—all stratified by age cohort. There was a striking decline in sexual interest, capacity for orgasm and coital frequency from age 38 to 54. Not all women reported a decrease, but the majority of the menopausal women did. The Gothenburg Women Study refuted a century-old belief that sexual interest abruptly increases during the climacteric. Although a small group reported increases in sexual interest or capacity for orgasm, the numbers were small and decreased with age.

The Danish study of Koster and Garde involved a general population sample of 474 women, all born in 1936, who were subsequently examined at the ages of 40, 45, and 51.[14] Personal interviews were conducted in 1976 and 1981, and questionnaires were mailed for the last followup. Of the 51-year-old women, 59 percent reported no change in sexual desire over the study period of 11 years, 30 percent reported decreased desire, and 11 percent reported an increase. However, this was based on recall from 11 years earlier. Decrease in sexual desire correlated significantly with the woman's subjective assessment of being climacteric.

One of the more recent investigations was by Hallstrom and Samuelsson, who utilized the women in the original Swedish cross-sectional study for a prospective study on sexual desire.[15] The study surveyed 497 married or cohabiting women, on two occasions, 6 years apart, about their sexual desire. They found significantly decreased sexual desire between ages 46 and 60. After the age of 50 years, none reported a strong sexual desire; 27 percent reported a decrease, and 10 percent reported an increase in desire between the interviews.

To assess what changes women complained of, Osborn et al. surveyed 436 women with a male sexual partner (94 percent married) and found 33 percent to have at least one operationally defined sexual dysfunction. (See sec. 6).[16] The most frequent dysfunctions were reduced sexual interest (17 percent), vaginal dryness (17 percent), and infrequent orgasm (16 percent). Dyspareunia was described by 8 percent. Significant factors were assessed, with age emerging as the most important determinant of operationally defined dysfunction. One or more dysfunctions occurred in 49 percent of women aged 50 and older and in 21 percent of women younger than age 50.

In 1997, Barlow et al. reported on their study of 2,045 women between the ages of 55 and 85 years.[17] Their aim was to describe urogenital aging and its associated problems in older British women. The survey reported 73 percent of the women were not sexually active, with the lack of a partner being a major reason. There was decreasing sexual activity with increasing age; however, women aged 65–74 had a frequency of activity similar to the younger women studied. Dyspareunia and/or vaginal dryness were described as a severe problem by 12 percent, among which 33 percent did not seek professional advice and 36 percent used "over-the-counter" remedies. HRT was of short duration and declined with age.

2.1 Influence of Menopausal Status and Ethnicity on Sexuality

Sarrel and Whitehead were among the earliest to associate a decline in sexual activity with menopause. They interviewed 185 women attending a menopause clinic to define what issues, concerns, and dysfunctions were present.[1] More than 86 percent reported a sexual problem. Most women (121/185) reported developing their sexual problem immediately preceding and following the transition through menopause. Problems they identified included disorders of sexual desire, sexual response, and sexual behavior. Newman and Nichols also showed a decline in sexual interest with age, with an implied association with the menopause transition.[10] In contrast, Pfeiffer et al. reported that, in comparison to age, menopausal status made a small contribution.[11]

In 1996, Myers performed a meta-analysis of sexuality and menopause.[18] Empirical studies performed from 1972 to 1992 that assessed sexuality and perimenopausal and postmenopausal women were collected and reviewed. A blinded review of the methodologies was performed. The findings of the analysis of viable studies indicated that hormones, both exogenous and endogenous, had some importance to perimenopausal and postmenopausal sexuality, suggesting an influence of sex hormones on menopausal sexuality.

It makes sense intuitively that there are ethnic variations in sexual function at menopause; however, few reports address this important issue. The most common complaints of naturally postmenopausal Thai women are loss of libido, orgasmic dysfunction, and dyspareunia.[19] Menopausal status appeared to impact sexual function, as both sexual desire and activity decreased after menopause. Only 14 percent occasionally reached an orgasm, while the other 86 percent never had orgasm after menopause.

Although many studies suggest some relationship, albeit ill-defined, between sexuality and menopause, Cawood and Bancroft did not concur. They recruited 141 women into a survey study of the determinants of sexuality and well-being in the menopause.[20] They found no relationship between menopausal status and interest or frequency of sexual activity and no support for the direct role of estrogens or androgens in the sexuality of women between the ages of 40 and 60. Only 54 women in their study were menopausal. Testing for hormone levels did not significantly predict measures of sexuality, while other aspects of the sexual relationship that were predictive were sexual attitudes and measures of well-being. They also identified vaginal lubrication as an important factor in the sexuality of women of this age group.

2.2 Summary

It is difficult, if not impossible, to separate the effect of aging effects on sexual function from that of menopause. Also, the menopausal transition is a time of psychosocial as well as biological change. It appears that there is a decline in sexual function as women age, but whether these changes are due to aging, the hormonal changes of menopause, psychosocial factors or health status remains uncertain. The most frequent complaints of women were reduced sexual interest, vaginal dryness, infrequent orgasm and dyspareunia.

3. Causes of Decreased Sexual Interest

Controversy exists over whether a reduced level of sexual interest is the cause of, or is caused by, infrequent or decreasing sexual activity in women or a decline in estrogen and/or androgen levels. Adaptation theory postulates a declining interest of the husband induces a similar response in the woman. Seemingly, the most common cause of declining sexual drive in men is age. However, the Gothenburg Study[15] showed no difference between the husbands of women with declining sexual interest and those with no change. In fact, a higher percentage of the women with declining interest reported that their partners' sexual interest was stronger. The same group admitted to submitting to their husbands' desire for intercourse without having desire themselves.

The most frequent complaints of women were reduced sexual interest, vaginal dryness, infrequent orgasm, and dyspareunia.

Zumoff et al. observed that endogenous androgens may play an important role in psychosexual functioning in the menopausal transition, during which testosterone levels are approximately 50 percent of the levels between 20 and 30 years of age.[21] Two studies have shown a correlation between endogenous androgen levels and optimal sexual function. McCoy et al.[22] evaluated 16 perimenopausal women who recorded their menstrual and sexual activity daily. Estradiol and testosterone levels showed significant declines during the menopausal transition; however, testosterone showed the most consistent association with coital frequency. Floter et al.[23] used the McCoy questionnaire to correlate the total score (for sexual enjoyment, orgasm, frequency, and vaginal state) with levels of testosterone, dehydroepiandrosterone sulfate, androstenedione, and the ratio of testosterone to SHBG (an indicator of free testosterone).[23] Androstenedione correlated with increased sexual functioning of perimenopausal women.

Many studies of sexual interest in premenopausal women suggest a cause-effect relationship between hormone levels and sexual function. Schiavi found a relationship between circulatory androgens and sexual desire and arousability in a large group of reproductive-aged women with regular menstrual cycles.[24] A higher sex drive at midcycle, during the testosterone peak, has been reported; however, it is difficult to relate these changes in sexuality to a single factor.[25]

4. Changes In Sexual Behavior, Interest, and Response

The cross-sectional baseline study of the Melbourne Women's Midlife Health Project surveyed 1,879 women by telephone with three aims: to describe women's subjective assessment of the changes that they experienced in sexual interest and reasons for those changes; to relate changes in interest, coital frequency, and dyspareunia with menopause; and to attempt to identify those variables that are associated with change in sexual behavior.[26] The majority reported no change in interest (62.3 percent), while a large number (31.1 percent) reported a decline in interest associated with menopause rather than age. Only 6.6 percent of women reported an increase in sexual interest. Natural menopause was associated with decreased interest and likelihood of intercourse and an increase in dyspareunia. Hysterectomy, with or without oophorectomy, had little influence on sexual activity.

Subsequently, 354 of these women participated in a longitudinal study and reported menopausal status significantly affected vaginal dryness and dyspareunia.[27] There was also an effect on sexual responsivity mediated through symptoms and well-being. Feelings for partner, sexual responsivity, frequency of sexual activities, and libido all significantly decreased with time, while vaginal dryness/dyspareunia and partner problems increased.

Another common condition that impacts sexual functioning is urinary and fecal incontinence. In a report by Hilton, 46 percent of women reporting UI felt that it had a negative impact on their sexual functioning.[28]

5. Anatomic and Physiologic Changes Associated with Aging

Masters and Johnson described how anatomic and physiologic changes associated with aging could negatively affect sexual response.[29] It may take a longer time to reach the excitement phase because of a reduction in the blood flow to the vagina, a reduction in engorgement of the genital organs, including the clitoris, as well as decreased amount of vaginal lubrication and a delay in time to lubrication. These factors may cause dyspareunia. The plateau phase may be prolonged as a result of reduced uterine elevation, decreased nipple erection, and vasocongestion of the breasts. Although orgasmic capacity is retained, there is a reduction in the number and intensity of vaginal contractions.

6. Defining Sexual Dysfunction

Classically, the definitions of female sexual dysfunction have been modeled on the human sexual response cycle first described by Masters and Johnson[29,30] and later enriched by Kaplan.[31] Their work formed the basis for the diagnostic systems of both the International Statistical Classification of Diseases and Related Health Problems (ICD–10)[32] and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV).[33] Recently, the Sexual Function Health Council of the American Foundation for Urologic Disease convened a consensus panel to reevaluate and better define and classify female sexual dysfunction.[34] Retaining the categories of both systems, several changes were made in the definitions and classifications; the new format is shown

below. One of the major changes in the classification schema was to add the criterion of personal distress to the diagnosis.

1999 Consensus Classification System

Sexual Desire Disorders

Hypoactive Sexual Desire Disorder

Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress. This allows for trigger of sexual desire to be secondary to the partner's initiative. If the choice is made to not be sexual, there is no disorder present.

Sexual Aversion Disorder

Sexual aversion disorder (SAD) is the persistent or recurrent phobic aversion and avoidance of sexual contact with a sexual partner, which causes personal distress. Because often this disorder is secondary to sexual or gynecologic trauma, some experts believe that it belongs in the category of phobias.

Sexual Arousal Disorders

A sexual arousal disorder is a persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement or genital (lubrication/swelling) or other somatic responses. Goldstein and Berman theorize that the etiology in some women experiencing difficulties with vaginal engorgement or clitoral erectile insufficiency may be secondary to atherosclerosis.[35]

Orgasmic Disorder

Orgasmic disorder is a persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress. This disorder occurs in 20–30 percent of women, not infrequently with vaginal intercourse.

Sexual Pain Disorders

Dyspareunia

Dyspareunia is a recurrent or persistent genital pain associated with sexual intercourse. The prevalence of this disorder has been reported to affect between 10–15 percent of women.[36] Consideration should be given to physical causes such as endometriosis, episiotomy scarring, or skin sensitivity.

Vaginismus

Vaginismus is a recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina, that interferes with vaginal penetration, which causes personal distress. Vaginismus occurs in 12–17 percent of all women in reports from the United States. However, in Asia, it is very rare to see it (Kim WW, personal communication).

Other Sexual Pain Disorders

Other sexual pain disorders are recurrent or persistent genital pain induced by noncoital sexual stimulation.

Each of the categories above has the following subtypes on the basis of the medical history, physical examination, and laboratory tests:

a) Lifelong versus acquired.

b) Generalized versus situational.

c) Etiologic origin (organic, psychogenic, mixed, unknown).

Health care professionals and the lay public are encouraged to implement this new classification system in the conduct of future research, the clinical diagnosis and treatment of women with sexual dysfunction, and the education of women with these problems.

7. Assessing Sexual Activity

Clinicians should routinely ask their patients about their sexual functioning. Many elderly couples wonder if it is still possible or safe to have coitus after the menopause or how long they can enjoy sex without harming their health. Sexual history questions particularly pertinent to postmenopausal patients include the following:

- Are you satisfied with your sexual life?
- Do you have any questions about sex?
- Has there been a change in your sex drive, lubrication, or orgasm?
- Do you have any sexual problems? Would you like help with the problem or problems?
- Can you describe when the problem started, and how often it occurs?
- Have you tried anything to correct the problem? Has it worked?
- Does your partner have any sexual problems?

It is important to be alert to the possible effects of aging, illness, or medical or surgical treatment on libido and sexual responsiveness. Sexual dysfunctions may have a negative influence on a woman's self image, her physiologic response, or her partner's response. One of the most controversial issues is whether hysterectomy impacts sexual function. If done for symptoms, such as pain or bleeding, a hysterectomy can result in improved sexual functioning.[37] Alternatively, some women view it as causing a loss of their female identity that negatively impacts sexual functioning.[38,39] Possible medical causes of sexual problems include the following:

Illnesses: Any physical or emotional chronic disease—physical or emotional, including liver, renal, cardiac, anemia, hypertension, stroke, cancer, neurologic disease, colostomy, neostomy, bladder surgery, incontinence, herpes virus or HIV infection, venereal warts, and cystitis—may cause sexual dysfunction.

Medications: Hypoglycemic agents, antihypertensive drugs, vasodilator and other cardiac drugs, antineoplastic drugs, major or minor tranquilizers (depending on dose), diuretics, and antihistamines may cause sexual problems. (See table 7–2.) Some studies suggest antidepressants (including SSRIs) may reduce desire and delay orgasm.[40] Decreased libido occurs in 20 percent of patients on tricyclic antidepressants, and 30 percent have impaired orgasm.

Treatments: Major surgery (hysterectomy, mastectomy, coronary artery bypass, organ transplant), dialysis, radiotherapy, and chemotherapy may cause sexual dysfunction.

8. Treatment For Sexual Dysfunction

Sexual function for any person at any age involves sexual thoughts, desires, feelings of arousal, potential for orgasm, and physical and mental relaxation. The treatment of sexual dysfunction is dependent adequate research showing efficacy of the treatment over another medication, a placebo or another treatment. Compared to with treatments for other mental health diagnoses, treatment for sexual dysfunction has lagged behind. The causes are multiple and include such issues as a lack of a standardized approach to therapy, the lack of control groups, and the dominance of the techniques described by Masters and Johnson.[30] However, one of the most probable causes for the lack of treatment options for sexual dysfunction has been the lack of research funding to study these disorders.

Behavioral and medical treatments for sexual dysfunction are reviewed below, and where evidence exists, recommendations are made as appropriate.

8.1 Behavioral Therapy for Sexual Dysfunction

A literature review of the application and outcome of sex therapy and other treatments for sexual dysfunction showed the format of effective conjoint sex therapy may be of significant benefit to couples with sexual dysfunction.[41] Sarwer and Durlak con-

TABLE 7–2

Medications Associated With Adverse Effects on Female Sexual Function and Response

Antihypertensive drugs
Antidepressants and anxiolytics (especially SSRIs)
Anti-inflammatory drugs
Antiparkinsonian drugs
Antiseizure drugs
Beta-blockers
Bromocriptine (painful clitoral tumescence)
Cimetidine
Digoxin
Diuretics
Gemfibrozil
Gonadotropin-releasing agents
Methyldopa
Psychoactive drugs
Sleeping pills
Tranquilizers

Abusive Drugs Associated with Abnormal Sexual Response

Alcohol
Narcotics
Nicotine

ducted a field trial of behavioral sex therapy for 365 married couples presenting with a range of sexual dysfunctions at an outpatient sexual dysfunction clinic of a large medical center.[42] The number of sensate focus exercises completed in the last week of treatment was the strongest predictor of successful treatment. The results of this study confirmed that behavioral sex therapy is effective in the treatment of married couples with sexual dysfunction.

8.1.1 Anorgasmia

The approach to treatment of primary anorgasmia utilizes the techniques of sensate focus, desensitization, and/or directed masturbation exercises. The primary elements of sensate focus developed by Masters and Johnson are physical caresses coupled with nonsexual progressing to sexual touching exercises.[30] The success rate was 84 percent in just over 1 year and 82 percent at 5 years. Desensitization is used when anxiety plays a major role in the dysfunction; however, it alone does not improve orgasmic capacity.[43] Directed masturbation exercises have had varying success in the treatment of primary anorgasmia.

Kilmann et al. investigated the differential effectiveness of various treatments for 55 couples where the woman reported secondary orgasmic dysfunction.[44] Compared with women in the control group, a significantly greater number of treated women reached or exceeded the project's 50-percent criterion for coital orgasmic functioning. However, these differences were not significant at the followup visit.

None of these studies evaluated the effects of treatment of individuals without partners and of, combining sex therapy with marital therapy and with physical methods of treatment. Thus, no evidence-based recommendations can be made.

A thorough review of behavioral therapies for sexual dysfunction is beyond the scope of this review but is available.[45]

9. The Influence of Endogenous Hormones and Exogenous Hormone Therapy for Sexual Behavior, Interest, and Response

9.1 Endogenous Hormones

The influence of the sex hormones, including estrogens, androgens, and progestogens, in the menopause remains debatable.

Although estrogen and estrogen/progestin replacement therapy have been shown to be an effective treatment for vaginal atrophy, increasing vaginal lubrication, they have not been shown to consistently increase sexual desire or activity.

Two studies have shown the importance of adequate estrogen levels in maintaining genital health and vaginal lubrication and preventing insertional dyspareunia. Semmens and Wagner reported on 14 women between the ages of 51 and 70 years who had decreased vaginal pH, vaginal fluid, and vaginal blood flow, all of which improved with HRT.[46] Sarrel showed a correlation between serum estradiol levels (concentrations) and sexual dysfunction.[47] At a level of less than 50 pg/mL, women reported vaginal dryness, increased frequency and intensity of dyspareunia, pain with penetration and deep insertion, and burning, all of which were significantly bothersome.

At the cellular level, Ginkel et al. compared the vaginal pH and microbial environment in women before and after starting HRT.[48] With HRT, the vaginal pH became more acidic, there was an increase in superficial cells, and most importantly, there was a significant decrease in the number of anaerobes and an increase in Lactobacillus species in the vagina.

Similarly, in an interview survey of 52 perimenopausal women with adequate records, Cutler et. al. reported women with estradiol levels below 35 pg/mL described reduced coital frequency compared with those with levels greater than 35 pg/mL.[49] Women with higher estradiol levels had no complaints related to sexual desire, response, or satisfaction.

Additionally, in observational study, 59 healthy, postmenopausal women between 60 and 70 years of age were evaluated for sexual function.[50] Two-thirds were sexually active. The sexually active group reported higher levels of sexual desire, greater sexual satisfaction, more comfort in expressing sexual preferences, and greater premenopausal sexual satisfaction than women who were not sexually active. On pelvic examination, the sexually active group had less genital atrophy than the abstinent group. Of the hormones studied, higher serum levels of free testosterone were associated with reports of increased sexual desire.

9.2 Estrogen/Hormone Replacement Therapy

Although estrogen and estrogen/progestin replacement therapy have been shown to be an effective treatment for vaginal atrophy, increasing vaginal lubrication, they have not been shown to consistently increase sexual desire or activity.

In the 1970s, three double-blind studies on the effects of HRT on sexual response reported conflicting results. Campbell found vaginal dryness was significantly decreased with estrogen treatment compared with placebo, but participants noted no change in masturbation, orgasm, and frequency of coitus or coital satisfaction.[51] Previous reports by Utian[52] and Coope et al.[53] failed to show improve-

ment in sexual desire in surgically and naturally menopausal women with CEEs.

Fedor-Freybergh showed significant benefit of ERT on libido, sexual activity, satisfaction, pleasurable experience, sexual fantasies, and capacity for orgasm.[54] This was corroborated in a randomized, double-blind, placebo-controlled, crossover trial of estrogen and progestin, alone and in combination, which found beneficial effects of estrogen alone or combined with the progestin on sexual desire, enjoyment, orgasmic frequency, and vaginal lubrication.[55] There were no differences between groups in coital frequency.

In a more recent study of estrogen transdermal replacement therapy in postmenopausal women, there was an improvement in patient satisfaction with frequency of sexual activity, sexual fantasies, degree of enjoyment, vaginal lubrication, and lack of pain during intercourse, without impacting frequency of orgasm or sexual arousal.[56]

9.3 The Role of Androgens in Sexual Function and Estrogen/Androgen CoTherapy for HRT

The role of sex steroids, including androgens, in sexual function remains controversial. As previously discussed, sexual desire can be influenced by many factors. In addition, the decline in serum testosterone is not unique to the menopause. In a study of 33 healthy volunteers, 24-hour serum levels of testosterone decreased steadily between ages 20 and 50.[21]

Ovarian and adrenal changes associated with the menopause lead to a decline in all androgen concentrations, with androstenedione production decreased more substantially than testosterone production.[57] Postmenopausal women obtain most of their circulating estrogen from peripheral aromatization of these androgens. SHBG is an important determinant of sex steroid activity, since the unbound steroid fraction is the biologically active component. SHBG is increased by estrogens, decreasing biologically available androgen. SHBG is decreased by androgen, increasing biologically available androgen.[58] Applying the evidence from animal studies, this may influence sexual desire at the level of the CNS.[59,60]

Geist and Salmon, although not the first, were among the early investigators to supplement ERT with androgens.[61] They studied the effects of testosterone propionate administered twice weekly at a dose of 25 mg, starting on the 12th day of the menstrual cycles for its effects on menopausal symptoms. Maintenance doses of 10 mg of either testosterone propionate or methyltestosterone monthly thereafter were also studied. They found that menopausal symptom relief was particularly helpful in women on estrogen alone with menorrhagia and in those who only had partial symptom relief with estrogen.

Shortly thereafter, Greenblatt reported on the use of androgens for hot-flush relief and an added benefit of improving libido.[62] Again in 1950, Greenblatt and colleagues studied the safety and efficacy of multiple estrogen-androgen formulations in a prospective, double-blind, placebo-controlled, crossover study.[63] They reported improved well-being and libido, with better relief of hot flushes and other menopausal symptoms than either HRT or placebo. Additionally, those on estrogen-androgen reported less breast tenderness, pelvic congestion, and nausea. In 1950, Glass reinforced the benefit of testosterone on women's sexual response.[64] He reported that combination therapy with estrogen and androgen produced a "smoother transition" and "provides reassurance to the menopausal woman that she is not failing in her psychosexual life."

Sherwin and Gelfand published a case series of surgically menopausal women and confirmed earlier studies showing the role of androgens in the maintenance of sexual functioning.[65] Sexual arousal, desire, and fantasies increased in women with estrogen-androgen replacement therapy as opposed to estrogen alone. They also noted that the rates of coitus and orgasm were higher in the

estrogen-androgen group during the first two post injection weeks. Additionally, they performed a crossover study of 53 surgically menopausal women and showed that the major impact of androgen in women was on sexual motivation, not increased sexual activity. Although there has been concern about the potential of negative impact of androgens on lipids and heart disease, research has not confirmed any increase in risk secondary to the addition of androgens in HRT.[66,67]

Although there has been concern about the potential of negative impact of androgens on lipids and heart disease, research has not confirmed any increase in risk secondary to the addition of androgens in HRT.

Sarrel et al. reported in 1998 on 20 postmenopausal women unhappy with their estrogen/hormone replacement therapy regimen who were randomized to receive either esterified estrogens or esterified estrogens with androgen for 8 weeks.[68] They described significantly improved sexual sensation and desire after 4-8 weeks of double-blind treatment with estrogen and androgen. They showed increased SHBG in the estrogen-only group with decreased free androgens and showed the reverse in the estrogen-androgen group. This led to the explanation that improvement in sexual sensation and desire may be related to the increased availability of endogenous or exogenous androgens.

In a pilot case series of 17 nonresponders to oral ERT, estradiol-testosterone combination implants appeared to significantly improve libido, enjoyment of sex, the ability to climax, and the initiation of sex, as examined by an analog scale, in a majority of women.[69]

9.4 Other Agents

Newer hormonal agents in research trials have indicated a possible benefit in reducing vaginal dryness, which may impact sexual function. Tibolone, a preparation with weak estrogen, progestin, and androgen activity not yet released for use, was studied in 437 women with postmenopausal complaints; they showed improvement of vaginal dryness, similar to 17β-estradiol/norethisterone acetate, with fewer bleeding problems.[70] In an RCT of tibolone versus 17β-estradiol, sexual frequency, satisfaction, and enjoyment were significantly improved over estradiol alone.[71]

Bupropion is an antianxiety medication which appeared to increase libido and orgasm in combination with sertraline.[72] It may be used as an antidote in women who have sexual dysfunction while on SSRIs.[73,74] A dose of 150 mg of trazodone daily has been reported to increase sex drive in a woman postmastectomy with low sex drive.[75] A recent small study of oral phentolamine in six postmenopausal women with female sexual arousal disorder showed self-reported improvement of vaginal lubrication and pleasurable vaginal sensations and deserves future study.[76]

Although there has been much interest in the use of sildenafil (Viagra®) in the sexual dysfunction of women, the only published study on the efficacy of this agent for female sexual arousal disorder was not shown to improve sexual response in women receiving estrogen.

Herbal remedies for sexual dysfunction lack rigorous study. A few small trials have assessed efficacy. A drug-monitoring study investigated 12 weeks of treatment with St. John's Wort extract, one tablet three times daily (900 mg Hypericum, Kira), in 111 women from a general medical practice in Germany. Patients were between 43 and 65 years of age, and had climacteric symptoms characteristic of the premenopausal and menopausal state. The Menopause Rating Scale,[78] a self-designed questionnaire for assessing sexuality, evaluated

treatment efficacy. Sexual well-being improved after treatment with St. John's Wort extract.[79] Although there are anecdotal reports of other herbal agents, no clinical trials have been performed to date. Of interest, clinicians in Asia do not expect herbal remedies to be effective in treating a woman's sexual dysfunction, since after thousands of years of use of oriental medicine, they still could not find appropriate therapy, even for men (Kim WW, personal communication).

10. Conclusions

Multiple population-based studies imply a decrease in female sexual functioning associated with the midlife years, and there is growing evidence that this reflects hormonal changes of the menopausal transition rather than increasing age. Hormonal change is only one aspect of the many factors that impact sexual functioning. These include presence of a sexual partner, partner's age and health, length of the relationship, feelings towards the partner, level of past sexual functioning, social class, educational level, experience of physical or psychological ill health, stressors, employment, personality factors, and negative attitudes towards the menopause.

Changes in sexual behavior, interest, and response should be assessed in the office on a regular basis and a plan developed with the woman to address her needs. Therapeutic options include the use of estrogen and estrogen-androgen replacement therapy.

11. Future Needs

As life expectancy continues to increase, the challenge for the future will be to improve the quality of aging years. Sexual health and well-being is an important part of that quality of life. Future needs are to:

- Improve understanding of the natural hormonal changes that occur with aging and menopause.
- Understand the role of endogenous estrogens and androgens in the sexuality of women.
- Develop standardized methods to measure libido in women.
- Better define the determinants of sexual health, including sexual desire and arousal, in menopausal women.
- Increase understanding of the effect of medications on female sexuality in the menopause.
- Understand the role of therapeutic hormonal and nonhormonal agents in the treatment of sexual dysfunction.
- Improve the transmission of information about sexual health to postmenopausal women.

Changes in sexual behavior, interest, and response should be assessed in the office on a regular basis and a plan developed with the woman to address her needs. Therapeutic options include the use of estrogen and estrogen-androgen replacement therapy.

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